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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,772	04/10/2000	Tracy D. Wilkins	420522000100	3347

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	25

DATE MAILED: 07/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/545,772	Applicant(s) WILKINS ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,13-15,19,20,23-26,28-31,33,36-39 and 62-66* is/are pending in the application.

4a) Of the above claim(s) *64-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,13-15,19,20,23-26,28-31,33,36-39 and 62-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *24* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Upon further review and reconsideration, the finality of the rejection of the last Office Action, (paper no. 16 mailed July 12, 2002) is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39 and 62-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition or vaccine for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component wherein the said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile*, wherein the polysaccharide component is conjugated to the rARU of *Clostridium difficile* and said polysaccharide component is characteristic of a pathogenic microorganism other than *C. difficile* does not reasonably provide enablement for an immunogenic composition or vaccine for eliciting an immune response to a pathogenic organism which the composition comprises a recombinant protein and a polysaccharide component wherein said protein comprises the toxin A repeating units (rARU) of *Clostridum difficile,* wherein the polysaccharide component is not conjugated to the rARU of *Clostridum difficile* and wherein said polysaccharide component is characteristic of a pathogenic microorganism other than

C. difficile. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the immunogencity of the surface polysaccharides of bacterial pathogens is improved when these antigens are bound covalently to a carrier protein (i.e. a conjugate). The specification teaches that the approach to improving the immunogenicity of polysaccharide antigens is based on experiments defining the effects of attaching a hapten or an antigen that is poorly immunogenic by itself to a carrier protein (page 3). Example 3 of the specification teaches the synthesis of polysaccharide-rARU conjugates (pages 19-21). Examples 4-7 of the instant specification all show the use of polysaccharide-protein conjugates (pages 21-28). The instant specification does not enable the use of an immunogenic composition or vaccine that comprises a protein component and a polysaccharide component wherein the polysaccharide is not conjugated to rARU of *Clostridum difficile*. Applicants admit in their "Brief On Appeal" that "one of the problems encountered in immunizing subjects for protection against infection where the antigen is a polysaccharide is that such polysaccharides may not be sufficiently immunogenic alone to elicit an immune response" and "therefore, they require the use of an immunogenic carrier to aid in eliciting an immune response" (page 3).

The teachings of the prior art regarding the use of carrier proteins to enhance the immunogencity of capsular polysaccharides are cited below:

Robbins et al (*The Journal of Infectious Diseases, 1990, 161:821-832)* teach surface polysaccharides may serve both as virulence factors and as protective antigens for bacteria whose invasion of the blood is their primary pathogenic event (page 821, 1st column). Robbins et al teach surface antigens include capsular polysaccharides (CP) of both gram-negative and gram-positive bacteria and the lipopolysaccharides (LPS) of the gram-negative bacteria (page 821, 2nd column). Robbins et al teach that both CP and LPS have immunologic properties and LPS also has pharmacologic activities that limit their use as vaccines. Robbins et al teach that the development of synthetic schemes for preparing clinically acceptable polysaccharide-protein conjugates allow us to skirt these limitations and conjugates may be considered as haptenated proteins and provide reagents, formerly confined to experimentation in animals which we may study human physiology and disease (page 821, 2nd column). Anderson et al *(Journal of Clinical Investigation, 1985, p. 52-59)* teach that mature humans unlike experimental animals make good antibody responses to the purified capsular polysaccharides of many invasive species, however, immunocompetence to these polymers mature more slowly than to proteins and lipopolysaccharides. Anderson teaches that the conjugation of capsular antigens to protein carriers might circumvent the delay in maturation and thus be able to immunize infants (who are generally at higher risk than adults) (page 57, 1st column). Anderson et al teach that protein-coupled capsular antigens have been described as potential immunogens against *Neisseria meningitidis* and *Streptococcus pneumoniae* as well as Hib and enhanced antibody responses have been found in experimental animals. Fattom et al *(Infection and Immunity, July 1990, p. 2367-2374)*

teach that *Staphylococcus aureus* Type 5 and type 8 capsular polysaccharides did not elicit serum antibodies when injected into mice alone but did elicit antibodies when bound (conjugated) to *Pseudomonas aeruginosa* exotoxin A (see the Abstract). Fattom et al teach that conjugates of pneumococcus type 12F have both increased immunogenicity and acquired T cell-dependent properties including higher IgG antibody levels in adult volunteers and similar improvement in the immunogenic properties in mice and monkeys are conferred to Vi-protein conjugates (pages 2372-2373). Schneerson et al, *(Infection and Immunity, September 1992, p. 3528-3532)* demonstrate that pneumococcus type 14 capsular polysaccharide bound (conjugated) to pertussis toxin elicited antibodies in mice to levels estimated to be protective in human and also elicited neutralizing antibodies to pertussis toxin (see the Abstract).

The specification, the Applicant's Brief on Appeal and the prior art have taught that polysaccharides are poor immunogens when administered to animals alone but immunogenicity of these polysaccharides is greatly enhanced when they are conjugated to carrier proteins.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

In view of the teachings of the specification (or the lack thereof) and the teachings of the prior art there is lack of enablement for an immunogenic composition or vaccine for eliciting an immune response to a pathogenic organism wherein the composition comprises a recombinant protein and a polysaccharide component wherein said protein comprises the toxin A repeating units (rARU) of *Clostridum difficile,* wherein the polysaccharide component is not conjugated to a carrier protein (i.e. rARU of *Clostridum difficile*) and said polysaccharide component is characteristic of a pathogenic microorganism other than *C. difficile*. It is determined that there are no working examples commensurate in scope with the instant claims and there is no guidance provided in the specification as to how to make and use immunogenic compositions or vaccine compositions that comprise a recombinant protein and a polysaccharide component wherein the polysaccharide component is not conjugated to rARU of *Clostridum difficile*. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed because the prior art has taught that capsular polysaccharides require the use of conjugated protein carriers to enhance their immunogenicity.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39 and 62-63 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are

indefinite because they recite "characteristic of a pathogenic microorganism". It is unclear as to what applicant intends by "characteristic of a pathogenic microorganism". Clarification is required.

Status of Claims

4. No claims are allowed.

Conclusion

5. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
June 27, 2003

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